

INTERNATIONAL SEARCH REPORT

International Application No

PCT/IL2004/000920

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 C07K16/40 A61K39/395 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ANONYMOUS: "Phospho specific Antibodies" NACALAI TESQUE NEWS, [Online] vol. 12, 2001, pages 1-10, XP002315815 Retrieved from the Internet: URL:http://www.nacalai.co.jp/catalog/PDF/n o12.pdf> [retrieved on 2005-01-28] page 3	1-63
X	----- EP 1 201 765 A (AXXIMA PHARMACEUTICALS AKTIENGESELLSCHAFT) 2 May 2002 (2002-05-02) claims 1-28	1-63
X	----- WO 97/37016 A1 (YEDA RESEARCH AND DEVELOPMENT CO. LTD; WALLACH, DAVID; MALININ, NIKOLA) 9 October 1997 (1997-10-09) claims 1-49	1-63
	----- -/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 February 2005

Date of mailing of the international search report

04.11.2005

Name and mailing address of the ISA

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Authorized officer

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 26-30,52-59 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>LIN X ET AL: "MOLECULAR DETERMINANTS OF NF-KAPPAB-INDUCING KINASE ACTION" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 18, no. 10, October 1998 (1998-10), pages 5899-5907, XP002920401 ISSN: 0270-7306 page 5906 abstract</p> <p>-----</p>	1-63

CORRECTED VERSION

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

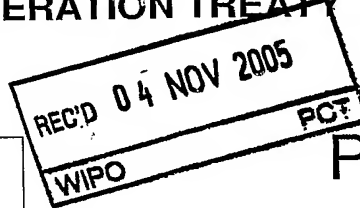
PCT/IL2004/000920

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 1201765	A	02-05-2002	NONE
WO 9737016	A1	09-10-1997	AU 732793 B2 03-05-2001
		AU 2175597 A	22-10-1997
		BG 102817 A	31-05-1999
		BR 9708518 A	03-08-1999
		CA 2250085 A1	09-10-1997
		CN 1221449 A	30-06-1999
		CZ 9803183 A3	12-05-1999
		EA 4309 B1	26-02-2004
		EE 9800322 A	15-04-1999
		EP 0894130 A1	03-02-1999
		HK 1018910 A1	05-08-2005
		HU 9902429 A2	28-10-1999
		JP 2000507826 T	27-06-2000
		NO 984551 A	24-11-1998
		NZ 331902 A	28-02-2000
		PL 329218 A1	15-03-1999
		SK 136198 A3	07-05-1999

PATENT COOPERATION TREATY

CORRECTED VERSION

From the
INTERNATIONAL SEARCHING AUTHORITY



PCT

To:

see form PCT/ISA/220

01111

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/IL2004/000920

International filing date (day/month/year)
05.10.2004

Priority date (day/month/year)
07.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07K16/40, A61K39/395, A61P37/00

Applicant
YEDA RESEARCH AND DEVELOPMENT CO. LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/IL2004/000920

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☒ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☒ in written format
 - ☒ in computer readable form
 - c. time of filing/furnishing:
 - ☒ contained in the international application as filed.
 - ☒ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 26-30,52-59

because:

- ☒ the said international application, or the said claims Nos. 26-30,52-59 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	2-11,14-25,31-44,46-51,60-63
	No: Claims	1,12,13,45
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25,31-51,60-63
Industrial applicability (IA)	Yes: Claims	1-25,31-51,60-63
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 26-30,52-59 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT) and no examination with regard to novelty and inventive step is performed (Art. 33(1) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

- D1: "Phospho specific Antibodies" NACALAI TESQUE NEWS, vol. 12, 2001, XP002315815 Retrieved from the Internet:
URL: http://www.nacalai.co.jp/catalog/PDF/n_o12.pdf > [retrieved on 2005-01-28]
- D2: EP-A-1 201 765 (AXXIMA PHARMACEUTICALS AKTIENGESELLSCHAFT) 2 May 2002 (2002-05-02)
- D3: WO 97/37016 A1 (YEDA RESEARCH AND DEVELOPMENT CO. LTD; WALLACH, DAVID; MALININ, NIKOLA) 9 October 1997 (1997-10-09)
- D4: LIN X ET AL: "MOLECULAR DETERMINANTS OF NF-KAPPAB-INDUCING KINASE ACTION" MOLECULAR AND CELLULAR BIOLOGY, AMERICAN SOCIETY FOR MICROBIOLOGY, WASHINGTON, US, vol. 18, no. 10, October 1998 (1998-10), pages 5899-5907, XP002920401 ISSN: 0270-7306

1 Novelty (Art. 33(2) PCT)

1.1 The document D1 discloses (the references in parentheses applying to this document): a catalog concerning antibodies specifically recognizing NF kappa B inducing kinase (NIK) with a phosphorylated Thr 559 residue (p. 3, lower table). It is also clear

from the same table that this antibody is useful for several immunological assays such as western blotting and immunohistochemistry. Therefore it is concluded that in view of D1 the subject-matter of independent claims 1,12,45 is not new in the sense of Article 33(2) PCT.

1.2 Claim 1 is broadly directed to all antibodies recognizing NIK or a fragment of NIK with a phosphorylated threonyl residue at position 559. It is well known that this represents the normal, active form of NIK (see D4 for info). Therefore any antibody specifically recognizing NIK in biological mixtures falls under the scope of claim 1. D2 discloses antibodies to a fragment of NIK which was able to detect NIK in western blot expression analysis. (example 8). Therefore the subject-matter of claim 1 is not new over D2 (Art. 33(2) PCT).

1.3 Independent claim 13 concerns a hybridoma clone characterised only by reference to its deposit number. However, the deposit number itself is not sufficient to distinguish this hybridoma from any other hybridoma. Therefore the subject-matter of this claim is not novel (art. 33(2) PCT).

2 Inventive Step (Article 33(3) PCT)

2.1 In the light of the novelty discussion of the claims above and in the light of the description of the present application (notably the examples and figures), claim 11 seems of particular interest. Therefore the presence of inventive step is assessed for this claim: D1, discussed above, discloses antibodies against Thr-559-phosphorylated NIK. The difference between claim 11 and D1 is the fact that the antibodies are monoclonal. The advantages of monoclonal antibodies are obvious to the person skilled in the art. He would therefore without applying inventive skill set out to modify the prior art relating to polyclonal antibodies against phosphorylated NIK and arrive at the monoclonal antibodies of claim 11. It is not indicated anywhere in the application that there was a special technical obstacle to overcome or an unexpected effect associated with the solution of the present application. Therefore it is concluded that the subject-matter of independent claim 13 lacks inventive step (Article 33(3) PCT).

It is noted that the applicant investigated the properties of the antibodies cited in D1 (p. 8, lines 3-7 of the present application). However, contrary to the applicants statement, the catalog number seems still to be available up till the data of establishment of the International search report. Moreover, the applicant fails to provide compelling evidence for differences with the prior art that could form the basis of acknowledging inventive step (Art. 33(3) PCT).

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

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2.2 Independent claims 14,31,37,47,60,62,63 refer to subject-matter which with regard to inventive step, are dependent on the presence of inventive step of the NIK antibody. In the light of D1 as discussed above, these claims can therefore not be considered as inventive.

2.3

Dependent claims 2-11,15-25,32-36,38-44,46,48-51,61 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, see documents D1-D4 and the corresponding passages cited in the search report.